REMARKS

Claims 1-6, 9 and 16-20 are all the claims pending in the application.

I. Claim Objections

Claims 1-6 are objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Specifically, the Examiner states that claims 1-6 further limit the use of the compounds recited in claim 9 as opposed to further limiting the structural description of the claimed compounds.

Applicants have amended dependent claims 2-6 herein. Applicants respectfully submit that the dependent claims further limit the subject matter of independent claim 9, since the therapeutically effective amount for the recited activity in the dependent claims is different from the broader therapeutically effective amount for the recited activity in claim 9, which would be apparent to one of ordinary skill in the art based upon the present specification. *See* Examples 4-8. Accordingly, Applicants respectfully request withdrawal of the objection.

II. Claim Rejections Under 35 U.S.C. § 103

Claims 1-6 and 9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sano et al (U.S. 5,516,919) in view of Fahim (U.S. 4,372,296) or Schinitisky (U.S. 4,938,969).

Applicants respectfully traverse the rejection. In the previous response, on November 30, 2001 (executed Declaration submitted on January 16, 2002), Applicants submitted a Declaration Under 37 C.F.R. § 1.132, showing unexpectedly superior results of the claimed invention based upon a comparison of the inhibitory effect of ascorbic acid-2-phosphate zinc salt as claimed when compared to other ascorbic acid phosphate salts. In the Office Action dated April 9, 2002, the Examiner indicated that the Declaration was not found to be persuasive allegedly because the

statements made in regard to Experiments 2-7 did not provide factual support of the unexpected superiority of the claimed invention. In view thereof, Applicants respectfully submit herewith, three (3) references which support the evaluation method of the irritation tests used in the Declaration filed on November 30, 2001 (executed Declaration submitted on January 16, 2002):

1. Roger J. Gay, et al, "The Living Dermal Equivalent As An In Vitro Model For Predicting Ocular Irritation, J. Toxicol. Cut. & ocular Toxicol., 11(1), 47-68 (1992) (Abstract);

2. Daniel Bagley, et al, "The SDA Alternatives Program Phase III: Comparison of In Vitro Data with Animal Eye Irritation Data on Solvents, Surfactants, Oxidizing Agents, And Prototype Cleaning Products", J. Toxicol. Cut. & ocular Toxicol., 13(2), 127-155 (1994) (Front Page);

3. S. D. Gettings, et al., "The CTFA Evaluation of Alternatives Program: An Evaluation of In Vitro Alternatives to the Draize Primary Eye Irritation Test (Phase II) Oil/Water Emulsions", Fd Chem. Toxic., Vol. 32, no. 10, pp. 943-976 (1994) (Front Page).

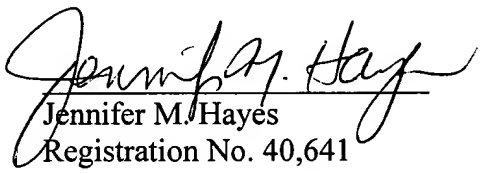
In view thereof, Applicants respectfully request reconsideration of the previously filed Declaration and withdrawal of the rejection.

III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims are amended as follows:

2. (Twice Amended) A dermal agent according to claim ~~9~~1, said dermal agent having activity as an antibacterial.

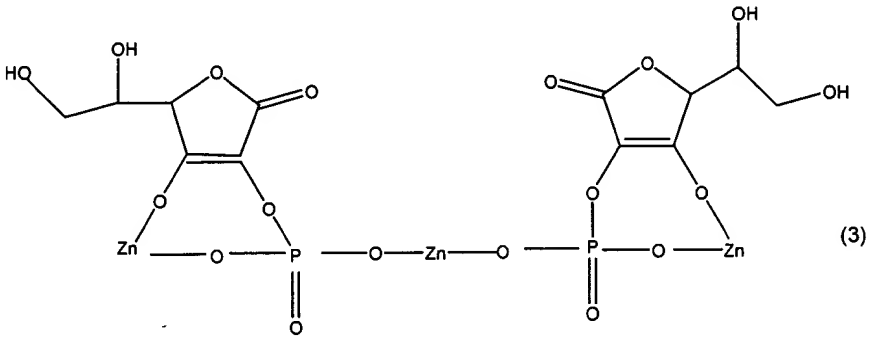
3. (Twice Amended) A dermal agent according to claim ~~9~~2, said dermal agent having an inhibitory effect on growth *of Propionibacterium.*

4. (Twice Amended) A dermal agent according to claim ~~9~~2, said dermal agent having an inhibitory effect on *Staphyloccocus.*

5. (Twice Amended) A dermal agent according to claim ~~9~~1, said dermal agent having inhibitory activity against lipase derived from microorganisms.

6. (Twice Amended) A dermal agent according to claim ~~9~~1, said dermal agent having inhibitory activity against hyaluronidase derived from microorganisms.

9. (Twice Amended) A dermal agent comprising a therapeutically effective amount of a compound which liberates ascorbic acid in vivo represented by the following formula (3):



(3)

J. Toxicol.—Cut. & Ocular Toxicol., 11(1), 47–68 (1992)

THE LIVING DERMAL EQUIVALENT AS AN IN VITRO MODEL FOR PREDICTING OCULAR IRRITATION

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Abstract

The Living Dermal Equivalent (LDE), composed of human dermal fibroblasts in a collagen-containing matrix, was used as a model system for examining toxic responses to a broad range of test chemicals and final product formulations. The thiazolyl blue (MTT) assay for mitochondrial function and the release of proinflammatory eicosanoids (prostaglandin E_2 and prostacyclin) were used as end points to rank order the relative irritancy of test samples. In these studies a total of 65 test samples including liquids, creams, emulsions, and solids were applied topically to the air-exposed surface of the LDE. Protocols were designed to maximize the discrimination between samples with known ocular irritation potentials. For a given set of samples, altering the experimental conditions, including the dosage and time of exposure, is shown to influence the degree to which responses of the LDE agree with in vivo data. Strategies for using the LDE as an in vitro ocular irritation model are presented and recommendations for standardized protocols are discussed.

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J. Toxicol.—Cut. & Ocular Toxicol., 13(2), 127–155 (1994)

THE SDA ALTERNATIVES PROGRAM PHASE III: COMPARISON OF IN VITRO DATA WITH ANIMAL EYE IRRITATION DATA ON SOLVENTS, SURFACTANTS, OXIDIZING AGENTS, AND PROTOTYPE CLEANING PRODUCTS

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This work was conducted by the Non-Animal Testing Research Subcommittee of the Biomedical Research Committee of The Soap and Detergent Association.

Pergamon

0278-6915(94)00075-1

Fd Chem. Toxic. Vol. 32, No. 10, pp. 943–976, 1994

0278-6915/94 $7.00 + 0.00

THE CTFA EVALUATION OF ALTERNATIVES PROGRAM: AN EVALUATION OF *IN VITRO* ALTERNATIVES TO THE DRAIZE PRIMARY EYE IRRITATION TEST. (PHASE II) OIL/WATER EMULSIONS

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(Accepted 15 April 1994)

Abstract—The Cosmetic, Toiletry and Fragrance Association (CTFA) Evaluation of Alternatives Program is an evaluation of the relationship between Draize ocular safety test data and comparable data from a selection of *in vitro* tests. In Phase II, 18 representative oil/water-based personal-care formulations were subjected to the Draize primary eye safety test and 30 *in vitro* assay protocols (14 different types of *in vitro* endpoints were evaluated; the remainder were protocol variations). Correlation of *in vitro* with *in vivo* data was evaluated using analysis of sensitivity/specificity and statistical analysis of the relationship between maximum average Draize score (MAS) and *in vitro* endpoint. Regression modelling is the primary approach adopted in the CTFA Program for evaluating *in vitro* assay performance. The objective of regression analysis is to predict MAS for a given test material (and to place upper and lower prediction interval bounds on the range in which the MAS is anticipated to fall with high probability) conditional on observing an *in vitro* assay score for that material. The degree of confidence in prediction is quantified in terms of the relative widths of prediction intervals constructed about the fitted regression curves: the narrower the prediction interval, the more predictive of the Draize score is the *in vitro* test result. 16 assays were shown to have the greatest agreement with the Draize procedure and were therefore selected for regression analysis. Based on the magnitude of the 95% prediction bounds of each of the 16 selected assays over the range of test data, it may be inferred that prediction of MAS values from experimentally determined *in vitro* scores is more accurate for oil/water-based formulations with lower rather than higher irritancy potential. The assays selected for modelling in Phase II generally exhibited weaker relationships with MAS than those selected in Phase I (evaluated using hydroalcoholic formulations), even though several assays were common to both Phases.

*To whom reprint requests should be addressed.

Abbreviations: AMA = alkaline membrane assay; BME = basal medium Eagle; CAM = chorioallantoic membrane; CAMA = chorioallantoic membrane assay; CAMVA = chori allantoic membrane vascular assay; CPSC = Consumer Product Safety Commission; CTFA = Cosmetic, Toiletry and Fragrance Association; DAQC = Data Analysis and Quality Control (Program); BMEM = Dulbecco's modified Eagle's medium; DMSO = dimethyl sulfoxide; EDE = Eytex/Draize equivalent; FCS = foetal calf serum; FHSA = *Federal Hazardous Substances Act*; HET-CAM = hen's egg test–chorioallantoic membrane; HSA = high sensitivity assay; HTD = highest t lerated dose; IS = irritati n score; KGM = Keratinocyte Growth Medium; LDE = Living Dermal Equivalent; MAS = maximum average Draize score; MDC = maximum days to clear; MEM = minimum Eagle's essential medium; NHEK = normal human epidermal keratinocyte; NR = neutral red; RMA = rapid membrane assay; UMA = upright membrane assay.